

**REMARKS*****Response to Restriction Requirement***

Applicants hereby elect the invention of Group III for prosecution in this application, designated by the Examiner as being claims to a method of treating cancer. All claims remaining in this application are directed to the elected invention.

The Examiner has additionally required that Applicants elect "a single anti-angiogenic agent from the list in claim 3 and a single inhibitor of the Src family of non-receptor tyrosine kinases from the list in claim 4." In response to this request for election of species:

- Applicants elect as the single species of anti-angiogenic agent the compound 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline, being the 2<sup>nd</sup> listed compound of original claim 3. Following entry of the above amendments, the claims readable on (specifically naming) this anti-angiogenic agent species are claims 13, 15, 18, 21 and 23, and claims 24-27 in that they are dependent on claims 13 and 23.
- Applicants elect as the single species of inhibitor of the Src family of non-receptor tyrosine kinases the compound 7-[2-(4-acetylpiperazin-1-yl) ethoxy]-4-(6-chloro-2,3-methylenedioxyanilino)-5-isopropoxyquinazolin, being the 7<sup>th</sup> listed compound of original claim 4. Following entry of the above amendments, the claims readable on (specifically naming) this species of inhibitor of Src non-receptor tyrosine kinase are claims 13, 17 18, 19 and 23, and claims 24-27 in that they are dependent on claims 13 and 23.

Following entry of the above amendments, claims readable on (specifically naming) both the elected anti-angiogenic agent species and the elected inhibitor of Src non-receptor tyrosine kinase are claims 13, 18 and 23, and claims 24-27 in that they are dependent on claims 13 and 23.

The Examiner has additionally required that Applicants elect a "single disclosed disease associated with angiogenesis from the list on page 8 of the specification." In

response to this further request for election of species, Applicants elect lung cancer.

Following entry of the above amendments, all pending claims are readable on (encompass) this species, and it is specifically recited in claims 24 and 26.

It is understood that the above two elections of species are provisional, such that upon the allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141.

### ***Claim Amendments***

Original claims 1-12 have been cancelled and new claims 13-27 have been added. All claims are now directed toward the elected subject matter of Group III, and Applicants reserve the right to prosecute the cancelled, non-elected subject matter in one or more divisional applications. Moreover, with the hope and expectation of expediting the prosecution of this application toward an early allowance, the present claims are directed toward a reduced scope of the elected method subject matter and to a reduced scope of the compounds administered in the elected method as explained further below. However, applicants reserve the right to prosecute any cancelled subject matter within the scope of the elected invention in one or more continuing applications.

Support for new claims 13-27 in the original specification and/or claims is as follows:

**New independent method claim 13** is directed toward the production of an anti-cancer effect by administration of a VEGF receptor tyrosine kinase inhibitor selected from three listed compounds, characterised in that (a) an improved anti-cancer effect is obtained and (b) an appropriate dose of each component of the combination is selected such that the contrasting blood pressure effects associated with the individual administration of either component of the combination are substantially counter-balanced.

Specific disclosure of this method is found in the specification, *e.g.*, at page 13, lines 15-22, with the understanding that a VEGF receptor tyrosine kinase inhibitor is an anti-angiogenic agent (see, *e.g.*, page 7, lines 13-17).

The three specific VEGF receptor tyrosine kinase inhibitor compounds that are listed in this claim are selected from original claim 3, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> listed VEGF receptor tyrosine kinase inhibitor compound in present claim 13 being the 1<sup>st</sup>, 2<sup>nd</sup> and 7<sup>th</sup> compounds, respectively, in original claim 3. The three specific Src kinase inhibitor compounds that are listed in this claim are selected from original claim 4, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> listed Src kinase inhibitor compounds in present claim 13 being the 5<sup>th</sup>, 7<sup>th</sup> and penultimate compounds in original claim 4.

**New claims 14-22** are dependent on claim 13, and direct the method of claim 13 toward administration of the 9 different combinations of one of the three VEGF receptor tyrosine kinase inhibitor compounds and one of the three Src kinase inhibitor compounds listed in present claim 13:

<b>Claim</b>	<b>VEGF RTK Inhibitor from Claim 13</b>	<b>Src Inhibitor From Claim 13</b>
14	1st	1st
15	2nd	1st
16	3rd	1st
17	1st	2nd
18	2nd	2nd
19	3rd	2nd
20	1st	3rd
21	2nd	3rd
22	3rd	3rd

**New independent method claim 23** parallels claim 13, except it is more specifically directed toward the treatment of a solid tumour disease by administration of a VEGF receptor tyrosine kinase inhibitor selected from three listed compounds, characterised in that (a) an improved anti-tumour effect is obtained and (b) an appropriate dose of each component of the combination is selected such that the contrasting blood pressure effects associated with the individual administration of either component of the combination are substantially counter-balanced.

Specific disclosure of this method is found in the specification, *e.g.*, at page 17, lines 7-14.

As with claim 13, the three specific VEGF receptor tyrosine kinase inhibitor compounds that are listed in this claim are selected from original claim 3, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> listed VEGF receptor tyrosine kinase inhibitor compound in present claim 13 being the 1<sup>st</sup>, 2<sup>nd</sup> and 7<sup>th</sup> compounds, respectively, in original claim 3. The three specific Src kinase inhibitor compounds that are listed in this claim are selected from original claim 4, the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> listed Src kinase inhibitor compounds in present claim 13 being the 5<sup>th</sup>, 7<sup>th</sup> and penultimate compounds in original claim 4.

**New claim 24** is directed to the method of claim 13 and lists specific cancers treatable by the method of claim 13, as listed in the specification at page 9, lines 26-32.

**New claim 25** is directed to the method of claim 13 or claim 23 wherein the VEGF receptor tyrosine kinase inhibitor and the Src kinase inhibitor are administered for the treatment of a solid tumour cancer as disclosed, *e.g.*, at page 8, lines 10-12.

**New claim 26** is directed to the method of claim 25 and lists specific solid tumours treatable by the method of claim 25, as listed in the specification, *e.g.*, at page 8, lines 10-12.

**New claim 27** is directed toward the method of claim 13 or claim 23 wherein the VEGF receptor tyrosine kinase inhibitor and the Src kinase inhibitor are administered simultaneously, sequentially or separately. Support for this claim and a discussion of the meaning of these terms is found, *e.g.*, at page 8, lines 18-33, wherein it is further noted that where the administration of the components is sequential or separate, the delay in administering the second component should not be such as to lose the benefit of the counter-balancing effect on blood pressure that is an aim of the combination therapy of the present invention. See also the discussion at page 43, lines 13-22 with respect to the simultaneous, sequential or separate administration of the components of the combination, noting that where the administration of these components is sequential or separate, the delay in administering the second component should not be such as to lose the benefit of a synergistic anti-cancer effect.

It should be clear from the above that no new matter has been added by these amendments, and entry thereof is believed to be appropriate and is respectfully requested. Following entry of these amendments, claims 13-27 are pending and all are directed toward the elected invention of Group III.

***Background and Explanation of Terms Used in the Claims***

The present invention is concerned with Applicants' discovery that the combined administration of an anti-angiogenic agent (here a VEGF receptor tyrosine kinase inhibitor) and a Src kinase inhibitor provides an improved anti-cancer or anti-tumour effect, and additionally that the Src kinase inhibitor at least in part counterbalances the blood pressure rise that follows administration of the anti-angiogenic agent. This dual effect of the combination is clearly set forth in the present claims. In an effort to expedite the prosecution of this application toward allowance, the claims now focus on combinations selected from three specifically named VEGF receptor tyrosine kinase inhibitor and three specifically named Src kinase inhibitors.

Specification support for the recitations in these claims is noted above. In addition, the Examiner's attention is respectfully called to the specification disclosure at *e.g.*, page 10, lines 15-24 with respect to meaning of the terms "anti-cancer" and "anti-tumour" effect and means that may be used to assess these effects, such as response rate, the time to disease progression and/or survival rate, and including inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment and slowing of disease progression. The Examiner's attention is further called to the specification disclosure at, *e.g.*, page 12, line 26 to page 13, line 7, with respect to the term "improved" anti-cancer effect as used in the claims. As there noted, a combination treatment is defined as affording an improved anti-cancer effect if the effect is synergistic, for example, where the effect is therapeutically superior to that achievable on dosing one or the other of the components of the combination treatment, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period. Further examples and guidance as to when the effect of the combination treatment is "improved" or synergistic are set forth in that paragraph and elsewhere in the specification.

As discussed at pages 4 through 6 of the specification, historically there have been inconsistencies in the art and confusion as to blood pressure effects of VEGF receptor tyrosine kinases and of Src non-receptor tyrosine kinases. However, as pointed out at, *e.g.*, page 11 of the specification in the paragraph extending from line 11 to line 25, anti-angiogenic agents that possess pharmacokinetic properties which provide reasonable bioavailability when administered chronically lead to an increase in diastolic blood pressure in the rat of about 10 to 30 mm Hg and in human beings of about 10 to 20 mm Hg. It is further noted that Src kinase inhibitors that possess pharmacokinetic properties which provide a reasonable bioavailability after a single dose lead to a decrease in diastolic blood pressure in the rat of about 10 to 25 mm Hg. Thus it will be appreciated, according to the invention, that the “contrasting blood pressure effects” associated with the individual use of either of an anti-angiogenic agent or of a Src kinase inhibitor will be “substantially counter-balanced” if the Src kinase inhibition reduces the hypertensive effect of the anti-angiogenic agent on diastolic blood pressure to less than about 10 mm Hg. It is further noted in that paragraph that the blood pressure effects will be “substantially counter-balanced” if the resultant diastolic blood pressure effect of appropriate doses of a combination of the anti-angiogenic agent and the Src kinase inhibitor is in the range of about -10 to +10 mm Hg.

In this regard, the Examiner's attention is also drawn to blood pressure study example discussed in the specification on pages 53 to 56 and in Figures 1 to 3 with respect to a combination of the VEGF receptor tyrosine kinase inhibitor described as VTK-1 {the compound 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)-quinazoline} and the Src kinase inhibitor described as Src-1 {the compound 7-[2-(4-acetylpiperazin-1-yl) ethoxy]-4-(6-chloro-2,3-methylenedioxyanilino)-5-isopropoxyquinazoline}. VTK-1 is the second VEGF receptor tyrosine kinase inhibitor named in claims 13 and 23, and is also the VEGF receptor tyrosine kinase inhibitor component named in dependent claims 15, 18 and 21. Src-1 is the second Src kinase inhibitor named in claims 13 and 23, and is also the Src kinase inhibitor named in dependent claims 17, 18 and 19. The data in Figures 1 to 3 in the specification, which illustrate the results of this Example, show that the contrasting blood

pressure effects of the VEGF receptor tyrosine kinase inhibitor VTK-1 and the Src kinase inhibitor Src-1 can be "substantially counter-balanced."

***Conclusion***

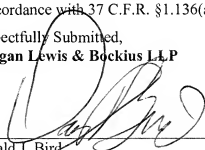
For the reasons discussed above, it is respectfully submitted that the new claims added by the above amendment are fully supported by the original specification and claims as filed; that the specification appropriately describes and enables the invention as presently claimed; that the specification provides the skilled person with sufficient guidance and/or definitions of the terms used in the claims to understand and use the claimed invention; and that all claims come within the scope of elected Group III. Accordingly entry of the claims presented above is believed to be in order, and entry and favorable consideration of all claims pending in this application are respectfully requested.

**Except** for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,  
**Morgan Lewis & Bockius LLP**

Date: February 7, 2008  
Morgan Lewis & Bockius LLP  
Customer No. **09629**  
1111 Pennsylvania Avenue, N.W.  
Washington, D.C. 20004  
Tel. No.: 202-739-3000  
DJB:db

By: \_\_\_\_\_

  
Donald J. Bird  
Registration No. 25,323  
Tel. No.: (202) 739-5320  
Fax No.: (202) 739-3001